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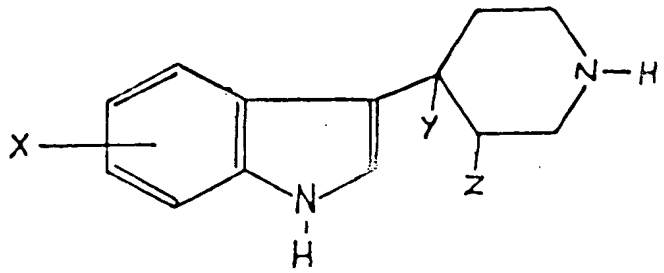
# (54) PIPERIDYL-INDOLE DERIVATIVES, PROCESSES FOR PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7eme, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to piperidyl-indole derivatives, processes for preparing them and pharmaceutical compositions containing them.

In one aspect, therefore, this invention provides piperidyl-indole derivatives, being compounds of general formula I:



I

(wherein X is a hydrogen, fluorine, chlorine or bromine atom, or an alkoxy group containing from 1 to 3 carbon atoms, and Y and Z are each a hydrogen atom or together form an additional carbon-carbon bond, with the proviso that X is not a hydrogen atom or alkoxy group when Y and Z are hydrogen atoms) and their acid addition salts.

The substituent X may be at any available position on the benzene nucleus of the indole, although the 4,5 and 6 positions on the indole moiety are preferred.

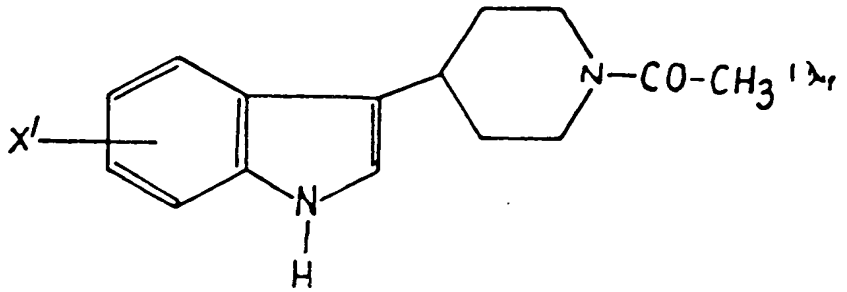
When X is an alkoxy radical it is advantageously a methoxy, ethoxy or *n*-propoxy radical.

The acid addition salts according to this invention are desirably formed with a pharmaceutically-acceptable mineral acid such as hydrochloric, hydrobromic, hydriodic, nitric, sulphuric or phosphoric acid, or equally well with a pharmaceutically-acceptable organic acid such as acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic or aspartic acid, an alkanesulphonic acid such as methane-sulphonic acid, or an arylsulphonic acid such as benzenesulphonic acid.

Amongst the piperidyl-indole derivatives defined hereinbefore, those in which X is a hydrogen atom or a methoxy group whilst Y and Z together form an additional carbon-carbon bond are preferred, and those in which Z is a chlorine atom whilst Y and Z are each a hydrogen atom, or together form a double bond, are particularly preferred.

Those compounds of general formula I and their salts described hereinafter in the Examples are specifically preferred piperidyl-indole derivatives of the invention.

In another aspect this invention provides a process for preparing the compounds of general formula I wherein Y and Z each represent a hydrogen atom, in which process a compound of general formula:

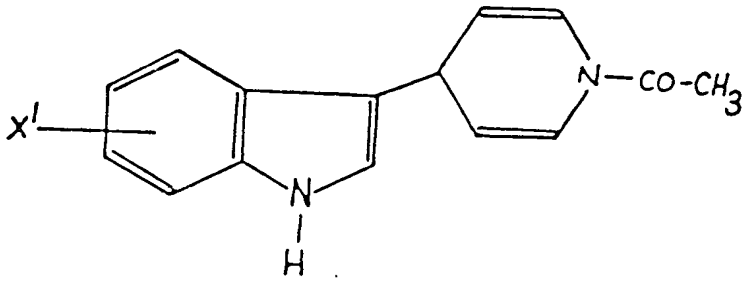


II

(wherein X' is a fluorine, chlorine or bromine atom) is saponified to form the desired product of general formula I.

The saponification of the compound of formula II is most conveniently performed by treatment with an alkali metal hydroxide, such as potassium hydroxide, in an alkanol, the alkanol preferably being propanol, and by refluxing the reaction mixture.

The starting materials of general formula II may be prepared by reduction of a compound of general formula:

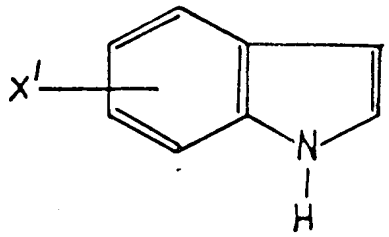


III

(wherein X' is as defined above) to give the desired product of general formula II.

The reduction of the compound of general formula III is advantageously performed by hydrogenation, employing a catalyst such as platinum oxide or palladium hydroxide.

Finally, the compounds of general formula III may themselves be prepared by reacting a compound of general formula:



IV

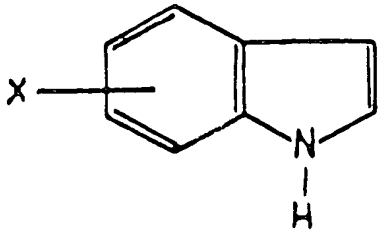
(wherein X' is as defined above) with pyridine and acetyl chloride to obtain the desired compound of general formula III.

The reaction is preferably performed in a medium of an ether such as dioxane or in acetic acid.

In a further aspect, this invention also provides a process for the preparation of the compounds of general formula I wherein Y and Z together form an additional carbon-carbon bond, in which process an acid addition salt of a compound of general formula I wherein Y and Z together form an additional carbon-carbon bond is treated with a base to form the desired compound of general formula I.

A concentrated ammonia solution is preferably employed as the base.

The acid addition salts used as starting material in this process may be prepared by reacting a compound of general formula:



IVa

(wherein X is as defined for general formula I) with an acid addition salt of 4-piperidone in acetic acid to form the desired acid addition salt of a compound of general formula I.

The acid addition salt of 4-piperidone employed in the above reaction is most conveniently a hydrohalide salt such as the hydrochloride.

Under preferred conditions for performing the preparation of the acid addition salts of general formula I, a strong acid, such as phosphoric acid, should be present in the reaction medium, and the reaction should be carried out between ambient temperature and the boiling temperature of the reaction medium.

The addition salts of the compounds of general formula I, wherein Y and Z together form an additional carbon-carbon bond, may be prepared using the reaction described above: otherwise, any of the salts of the invention may be prepared by salifying a compound of general formula I. Preferably the salification is carried out by reacting an acid in substantially stoichiometric proportions with the compound of general formula I.

The piperidyl-indole derivatives of the invention possess interesting pharmacological properties, showing remarkable antidepressive, antiparkinsonian and antiemetic acticity, which may make them useful in the treatment of psychic, behavioral and character disorders, or akinetic and dyskinetic conditions, as well as in the treatment of vomiting and nausea. However, before any of the derivatives of this invention may be used in medicine, they should preferably be formed into pharmaceutical compositions by association with suitable pharmaceutical vehicles.

Accordingly, in yet another aspect, this invention provides pharmaceutical compositions containing one or more of the compounds of general formula I, and/or their acid addition salts formed with pharmaceutically acceptable acids, in association with a suitable pharmaceutical vehicle.

The terms "pharmaceutical" and "pharmaceutically acceptable" are used herein to exclude any possibility that the nature of the vehicle, or of the acid, considered of course in relation to the route by which the composition is intended to be administered, could be harmful to the subject treated.

The compositions of this invention are preferably administered by the digestive or parenteral route, and in respect of these routes, the "pharmaceutical vehicle" is preferably:-

a) the ingestible excipient of a tablet, sugar-coated tablet, sublingual tablet or pill; the ingestible container of a gelatin capsule or cachet, or the ingestible pulverulent solid carrier of a powder.
b) a sterile injectable liquid solution or suspension medium, or
c) a base material shaped to form a suppository.

Whilst the forms of presentation just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

The exipients employed in the above forms are preferably those that are customarily employed in pharmaceutical peparations and may be solid or liquid materials such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, as well as other aqueous and non-aqueous liquid carriers, optionally compounded with various wetting, dispersing or emulsifying agents and/or preservatives.

Whilst the dosages of the pharmacologically active ingredient will, to a certain degree, depend upon the derivative used, the complaint concerned and the subject treated, nevertheless, by way of general indication, it may be said that the useful dose ranges from 5 mg to 500 mg of active principle per day for an adult, when administered by the oral route.

The preferred pharmaceutical compositions of this invention are of course those that contain the piperidyl-indole derivatives mentioned hereinbefore as being preferred.

The following Examples and Formulations are given, though only by way of illustration, to show some preferred aspects of the invention.

*Example 1: 5-chloro-3-(4-piperidyl)-1H-indole and its hydrochloride.*

*Stage A: 3-(1-acetyl-1,4-dihydro-4-pyridyl)-5-chloro-1H-indole.*

27 $cm^3$ of redistilled pyridine were added to 120 cm of dioxane and 11.2 $cm^3$ of acetyl chloride, which were cooled by a bath of iced water to maintain the temperature of the mixture at between 8 and 15°C. 22 g of 5-chloro-1H-indole in 120 $cm^3$ of dioxane were added to the suspension thus obtained, whilst maintaining the temperature between 10 and 15°C, and the mixture was agitated for 7 hours at ambient temperature in a darkened environment. The suspension obtained was then poured into 500 $cm^3$ of water, and agitated for 5 minutes before the addition of another 500 $cm^3$ of water. The mixture was filtered, and the solid separated was made into a paste with 40 $cm^3$ of acetonitrile, filtered, and rinsed with acetonitrile and then with ether

13.5 g of 3-(1-acetyl-1,4-dihydro-4-pyridyl)-5-chloro-1H-indole were obtained in the form of a pale yellow-coloured solid. (M.Pt. = 202°C).
*Analysis:* $C_{15}H_{13}Cl\ N_2O$ = 272.747

| | C% | H% | Cl% | N% |
|---|---|---|---|---|
| Calculated: | 66.06 | 4.80 | 13.0 | 10.27 |
| Found: | 66.0 | 4.9 | 13.1 | 10.4 |

*Stage B: 3-(1-acetyl-4-piperidyl)-5-chloro-1H-indole*

8.49 of 3-(1-acetyl-1,4-dihydro-4-pyridyl)-5-chloro-1H-indole and 850 mg of platinum oxide were introduced into 420 $cm^3$ of ethanol, and hydrogen was absorbed into the mixture until saturation. The solid formed was filtered, rinsed with ethanol and evaporated to dryness, to give 9 g of crude product. This was taken up with 10 $cm^3$ of acetonitrile, and after agitating for 20 minutes at ambient temperature, was filtered and rinsed with acetonitrile to give 6.99 g of 3-(1-acetyl-4-piperidyl)-5-chloro-1H-indole, which was purified by recrystallizing in ethanol. After drying, 4.78 g of 3-(1-acetyl-4-piperidyl)-5-chloro-1H-indole were recovered in the form of a colourless solid melting at 201°C.
*Analysis:* $C_{15}H_{17}Cl\ N_2O$ = 276.779

| | C% | H% | Cl% | N% |
|---|---|---|---|---|
| Calculated: | 65.1 | 6.19 | 12.81 | 10.12 |
| Found: | 65.2 | 6.3 | 12.6 | 10.1 |

*Stage C: 5-chloro-3-(4-piperidyl)-1H-indole and its hydrochloride*

6.02 g of 3-(1-acetyl-4-piperidyl)-5-chloro-1H-indole and 6 g of potassium hydroxide were introduced into 50 $cm^3$ of propanol. The mixture was refluxed for 4 hours, and then, after cooling, the solution obtained was poured into 500 $cm^3$ of iced water. The mixture was agitated for 45 minutes at ambient temperature, and the solid obtained was filtered, rinsed with water and dried under vacuum at 50°C to give 5.02 g of 5-chloro-3-(4-piperidyl)-1H-indole.
(M.Pt. = 208°C).

*Preparation of the hydrochloride.*

5.5 g of 5-chloro-3-(4-piperidyl)-1H-indole, prepared as indicated above, were put into suspension in 120 $cm^3$ of ethyl acetate. The suspension was chilled, agitated, and then 10 $cm^3$ of ethyl acetate were added before saturating with hydrochloric acid. The mixture was agitated for 15 minutes in an ice bath, and the solid obtained was filtered off and rinsed with ethyl acetate and then ether to give 5.89 g of the crude hydrochloride which was purified by recrystallization in ethanol. The product was rinsed with ethanol, then with ether, and dried under vacuum at ambient temperature to give 2.85 g of 5-chloro-3-(4-piperidyl)-1H-indole hydrochloride in the form of a colourless solid
(M.Pt. = 260-262°C).
*Analysis:* $C_{13}H_{16}Cl_2N_2$ = 271.198

| | C% | H% | Cl% | N% |
|---|---|---|---|---|
| Calculated: | 57.57 | 5.95 | 26.15 | 10.33 |
| Found: | 57.3 | 6.0 | 25.8 | 10.2 |

*Example 2: 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.*

10 g of indole were dissolved in 200 $cm^3$ of acetic acid and the solution was heated to 95-100°C under agitation and in an atmosphere of nitrogen. 50 $cm^3$ of N aqueous phosphoric acid and 39.3 g of monohydrated 4-piperidone hydrochloride were added, and the mixture was heated to 100°C for one hour, allowed to cool, and then poured onto ice, to which had been added 350 $cm^3$ of concentrated ammonia. The product was extracted with ethyl acetate, and the extracts were washed with water, then salt water, dried over magnesium sulphate, and evaporated to dryness to give 14.7 g of crude product, which were made into a paste, under nitrogen, with 75 $cm^3$ of methanol. The paste was filtered under vacuum and the solid obtained was rinsed with methanol, and then ether, to eventually obtain 1.42 g of 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole M.Pt. = 185-186°C.

The remaining mother liquor was evaporated off, and the residue was purified by chromatography on silica - eluting with a chloroform-methanol-triethylamine mixture (6:3:1) - to give 4.55 g of product (Rf 0.15), which was made into a paste with ether. Finally, 4.295 g of 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were obtained from the mother liquor, giving a total yield of 5.715 g, which was purified by recrystallisation in isopropanol

to give 3.56 g of 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole (M.Pt. = 190-191°C).

*Preparation of the neutral succinate.*

3.8 g of 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were dissolved in 200 $cm^3$ of methanol and 2.26 g of succinic acid were added. The formed succinate was recovered and redissolved in methanol, at reflux. The solution was filtered whilst hot then concentrated and allowed to crystallise. After carrying out a second purification by this method 2.65 g of 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole neutral succinate were obtained (M.Pt. = 238-240°C).

*Analysis:* $C_{30}H_{34}N_4O_4 = 514.60$

| | | | |
|---|---|---|---|
| Calculated: | C% 70.02 | H% 6.66 | N% 10.89 |
| Found: | 69.7 | 6.6 | 10.9 |

*Example 3: 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.*

At 100°C, 12.6 g of 5-methoxy-1H-indole were dissolved in 240 $cm^3$ of acetic acid, 44 g of monohydrated 4-piperidone hydrochloride were added and the mixture was maintained at 100°C for 30 minutes. After cooling, the mixture was poured onto iced water, to which had been added 400 $cm^3$ of concentrated ammonia. The product was extracted with ethyl acetate and the organic phase was washed with salt water, dried over magnesium sulphate and evaporated to dryness to give 20 g of crude product, which was purified by chromatography on silica, eluting with a chloroform-methanol-triethylamine mixture (7:2:1). 5.26 g of 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were obtained in the form of a resin.

*Preparation of the neutral succinate.*

5.26 g of 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were dissolved in 100 $cm^3$ of methanol, and 1.22 g of succinic acid dissolved in 10 $cm^3$ of methanol were added. The mixture was allowed to crystallise, and the crystals formed were filtered and rinsed with methanol, then with ethanol, to give 4.4 g of 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole neutral succinate in the form of crystals (M.Pt. = 255-258°C.)

*Analysis:* $C_{32}H_{38}N_4O_6 = 574.683$

| | | | | |
|---|---|---|---|---|
| Calculated: | C% 66.88 | H% 6.66 | N% 9.74 | |
| Found: | 66.6 | 6.8 | 9.6 | |

*Example 4: 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.*

9.05 g of 5-chloro-1H-indole were dissolved in 180 $cm^3$ of acetic acid, and the solution was heated to about 90°C before introducing 47.5 g of 4-piperidone hydrochloride monohydrate. The temperature was maintained at 90-100°C for one hour, after which the mixture was allowed to cool and then poured onto iced water, to which 300 $cm^3$ of concentrated ammonia had been added. The product was extracted with ethyl acetate, and the extracts were washed with water, then with salt water, dried over magnesium sulphate and evaporated to dryness to give 12.816 g of a crude product, which was taken up with a chloroform-methanol-triethylamine mixture (6:3:1). The solution formed was filtered under vacuum, and the filtrate was chromatographed on silica - eluting with a chloroform-methanol-triethylamine mixture (6:3:1). After evaporation of the eluant 5.973 g of 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were obtained in the form of a yellow resin.

*Preparation of the neutral succinate.*

5.973 g of 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole were dissolved in 50 $cm^3$ of methanol, 3 g of succinic acid were added, and crystals were allowed to form, and the mixture was chilled for 30 minutes. The crystals were separated by vacuum filtration, rinsed with methanol and dried to give 5.400 g of 5-cloro-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole neutral succinate in the form of yellow crystals (M.Pt. = 253-254°C).

*Analysis* $C_{36}H_{42}Cl_2N_4O_4 = 583.52$

| | | | | |
|---|---|---|---|---|
| Calculated: | C% 61.75 | H% 5.52 | Cl% 12.15 | N% 9.60 |
| Found: | 61.5 | 5.6 | 12.2 | 9.4 |

*Example 5: 4-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate*

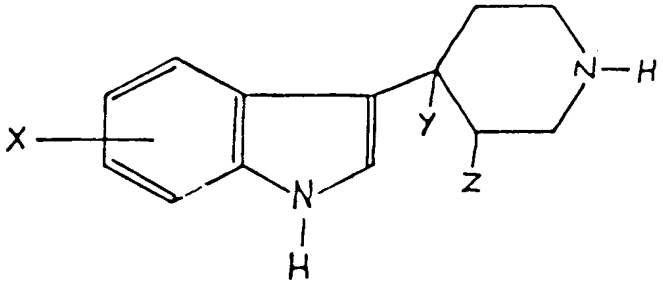
Operating as in example 3, but starting with 4-methoxy-1H-indole, 4-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole neutral succinate was obtained in the form of crystals M.Pt. = 160°C, then 194-196°C.

*Formulation 1*
Compressed tablets were prepared corresponding to the formula:
5-chloro-3-(4-piperidyl)-1H-indole hydrochloride 25 mg
Excipient q.a. for one compressed tablet up to 200 mg.

*Formulation 2* An injectable solution was prepared corresponding to the formula:
5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole neutral succinate 25 mg
Sterile aqueous excipient q.s.v. 2 ml.

WHAT WE CLAIM IS:

1. Piperidyl-indole derivatives, being compounds of general formula I:



I

(wherein X is a hydrogen, fluorine, chlorine or bromine atom, or an alkoxy group containing from 1 to 3 carbon atoms, and Y and Z are each a hydrogen atom or together form an additional carbon-carbon bond, with the proviso that X is not a hydrogen atom or alkoxy group when Y and Z are hydrogen atoms) and their acid addition salts.

2. An acid addition salt as claimed in claim 1, which is formed with a pharmaceutically-acceptable mineral acid.

3. An acid addition salt as claimed in claim 1, which is formed with a pharmaceutically-acceptable organic acid.

4. A piperidyl-indole derivative as claimed in any of the preceding claims, in which X is a hydrogen atom or a methoxy group whilst Y and Z together form an additional carbon-carbon bond.

5. A piperidyl-indole derivative as claimed in any of claims 1 to 3, in which X is a chlorine atom whilst Y and Z are each a hydrogen atom or together form an additional carbon-carbon bond.

6. 5-chloro-3-(4-piperidyl)-1H-indole and its hydrochloride.

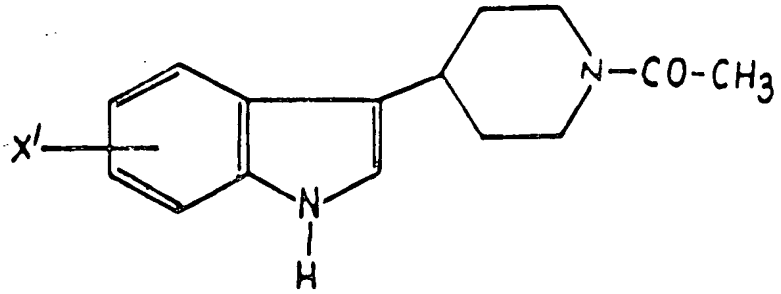
7. 3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.

8. 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate

9. 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.

10. 4-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1H-indole and its neutral succinate.

11. A process for preparing the compounds of general formula I as claimed in claim 1 wherein Y and Z each represent a hydrogen atom, in which process a compound of general formula:

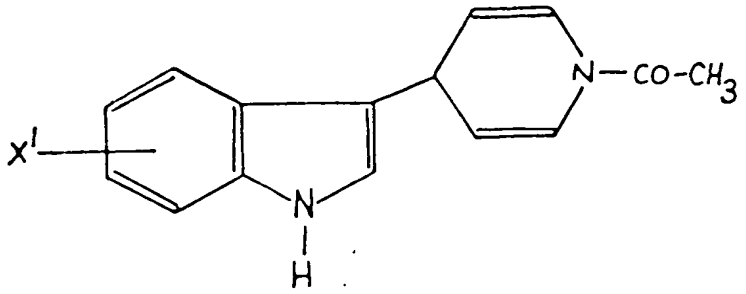


II

(wherein X' is a fluorine, chlorine or bromine atom) is saponified to form the desired product of general formula I.

12. A process as claimed in claim 11, in which the saponification is performed by refluxing the compound of general formula II with potassium hydroxide in propanol.

13. A process as claimed in claim 11 or claim 12, in which the starting material of general formula II is prepared by reduction of a compound of general formula

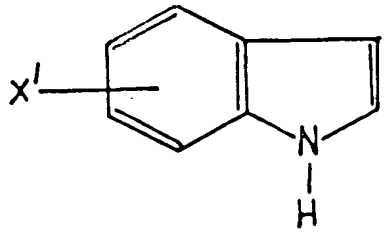


III

(wherein X' is as defined in claim 11) to give the desired product of general formula II.

14. A process as claimed in claim 13, in which the reduction is performed by hydrogenation, employing a platinum oxide or palladium hydroxide catalyst.

15. A process as claimed in claim 13 or claim 14, in which the compound of general formula III is itself prepared by reacting a compound of general formula:



IV

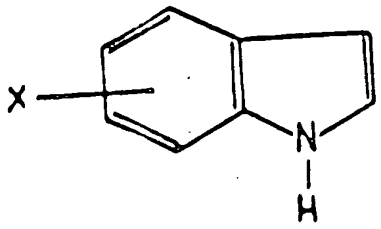
(wherein X' is as defined in claim 11) with pyridine and acetyl chloride to obtain the desired compound of general formula III.

16. A process as claimed in claim 15, in which the reaction is performed in dioxane or in acetic acid.

17. A process for preparing the compounds of general formula I as claimed in claim 1 wherein Y and Z together form an additional carbon-carbon bond, in which process an acid addition salt of a compound of general formula I wherein Y and Z together form an additional carbon-carbon bond is treated with a base to form the desired compound of general formula I.

18. A process as claimed in claim 17, in which a concentrated ammonia solution is employed as the base.

19. A process as claimed in claim 17 or claim 18, in which the acid addition salt starting material is prepared by reacting a compound of general formula:



IVa

(wherein X is as defined in claim 1) with an acid addition salt of 4-piperidone in acetic acid to form the desired acid addition salt of the compound of general formula I.

20. A process as claimed in claim 19, in which the acid addition salt of 4-piperidone is the hydrochloride salt.

21. A process as claimed in claim 19 or claim 20, in which phosphoric acid is present in the reaction medium, and the reaction is carried out between ambient temperature and the boiling temperature of the reaction medium.

22. A process for preparing an acid addition salt of a compound of general formula I as claimed in claim 1 wherein Y and Z together form an additional carbon-carbon bond as defined in any of claims 19 to 21.

23. A process for preparing an acid addition salt of a compound of general formula I as claimed in claim 1, in which a compound of general formula I is salified.

24. A process as claimed in claim 23, in which the salification is carried out by reacting an acid in substantially stoichiometric proportions with the compound of general formula I.

25. A process as claimed in claim 23 or claim 24, in which the compound of general formula I is prepared by a process as defined in any of claims 11 to 21.

26. A process for preparing a piperidyl-indole derivative, as defined in claim 1, substantially as described hereinbefore with reference to any one of the Examples.

27. A piperidyl-indole derivative when prepared by a process defined in any of claims 11 to 26.

28. Pharmaceutical compositions containing one or more of the compounds of general formula I as defined in claim 1, and/or their acid addition salts formed with pharmaceutically acceptable acids, in association with a suitable pharmaceutical vehicle.

29. A pharmaceutical composition as claimed in claim 28, which contains a piperidyl-indole derivative as defined in claim 4 or claim 5.

30. A pharmaceutical composition as claimed in claim 28, which contains a piperidyl-indole derivative as defined in any of claims 6 to 8.

31. A pharmaceutical composition as claimed in claim 28, which contains a piperidyl-indole derivative as defined in claim 9 or claim 10.

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